#5

PATENT
1199-1-005CIP2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT	:	Moses Rodriguez et al.		
SERIAL NO.	:	10/010,729	EXAMINER :	Unknown
FILED	:	November 13, 2001	ART UNIT :	1641
FOR	:	HUMAN IgM ANTIBODIES, AND DIAGNOSTIC AND THERAPEUTIC USES THEREOF PARTICULARLY IN THE CENTRAL NERVOUS SYSTEM		

CERTIFICATE OF MAILING UNDER 37 CFR 1.8

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to the ASSISTANT COMMISSIONER OF PATENTS, WASHINGTON, DC 20231 on September 20, 2002.

David A. Jackson, Reg. No. 26,742
(Name of Registered Representative)

Martha Bussard 9/20/02
(Signature and Date)

AMENDMENT UNDER 37 C.F.R. 1.115

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

Dear Sir:

In response to the outstanding Notice to File Missing Parts of Non-Provisional Application dated March 20, 2002, and in accordance with Rule 115 of the Rules of Practice, please consider the following amendments and remarks. Applicants submit concurrently herewith a Petition for Extension of Time for four months, up to and including September 20, 2002, accompanied by the required fee.

IN THE SPECIFICATION:

Please enter on the record after the abstract on Page 234 the sequence listing, a paper copy of which is attached for reference. The sequence listing, in both paper copy and computer readable form together with appropriate statements concerning identity of the two, are being filed

submissions.

Please substitute the following amended paragraph for the paragraph starting on Page 8, lines 18-30 and Page 9, lines 1-11:

More particularly, the antibodies comprehended within the scope of neuromodulatory agents of the invention may be selected from the group consisting of mAb SCH94.03, SCH79.08, O1, O4, O9, A2B5, HNK-1, sHIgM22 (LYM 22), ebvHIgM MSI19D10, sHIgM46 (LYM46), CB2bG8, AKJR4, CB2iE12, CB2iE7, MSI19E5, MSI10E10, mixtures thereof, monomers thereof, active fragments thereof, and natural or synthetic autoantibodies having the characteristics of the particular mAb SCH94.03, SCH79.08, O1, O4, O9, A2B5, HNK-1, sHIgM22 (LYM 22), ebvHIgM MSI19D10,sHIgM46 (LYM46), CB2bG8, AKJR4, CB2iE12, CB2iE7, MSI19E5 and MSI10E10. Antibodies further comprehended within the scope of the neuromodulatory agents of the invention are recombinant antibodies derived from mAb SCH94.03, SCH79.08, O1, O4, O9, A2B5, HNK-1, sHIgM22 (LYM 22), ebvHIgM MSI19D10, sHIgM46 (LYM46), CB2bG8, AKJR4, CB2iE12, CB2iE7, and MSI10E10. The present neuromodulatory agents may be derived from mammalian cells and specifically, may be derived from human cells. Further, the neuromodulatory agents may comprise a polypeptide having an amino acid sequence corresponding at least in part, to a sequence selected from the group consisting of FIGURE 35 (SEQ ID NO: 8,7), FIGURE 36 (SEQ ID NO: 10, 9), FIGURE 37 (SEQ ID NO: 11, 12), FIGURE 38 (SEQ ID NO:13, 14), FIGURE 45 (SEQ ID NO: 15, 16), FIGURE 46 (SEQ ID NO: 17, 18), FIGURE 55 (SEQ ID NO: 25, 26), FIGURE 56 (SEQ ID NO: 27, 28), FIGURE 57 (SEQ ID NO: 29, 30), FIGURE 58 (SEQ ID NO: 31, 32), FIGURE 59 (SEQ ID NO: 33, 34), FIGURE 60 (SEQ ID NO: 35, 36), FIGURE 61 (SEQ ID NO: 37, 38), FIGURE 71 (SEQ ID NO:49), FIGURE 72 (SEQ ID NO:51) and active fragments thereof. Recombinant or synthetic antibodies derived or based therefrom and corresponding at least in part to a sequence selected from the above group are further included in the present invention.

Please substitute the following amended paragraph for the paragraph starting on Page 9, lines 13-22:

The present invention thus relates to the monoclonal antibody sHIgM22 (LYM22), monomers thereof, active fragments thereof, and natural or synthetic antibodies having the characteristics of sHIgM22. Recombinant antibodies derived from sHIgM22 are further contemplated and are provided herein. The invention provides antibodies comprising a polypeptide having an amino acid sequence corresponding at least in part to a sequence selected from FIGURE 35 (SEQ ID NO: 8, 7) and FIGURE 36 (SEQ ID NO: 10, 9), and active fragments thereof. Recombinant or synthetic antibodies derived or based therefrom and corresponding at least in part to a sequence selected from SEQ ID NO: 8, 7, 10 and 9 are further included in the present invention.

Please substitute the following amended paragraph for the paragraph starting on Page 9, lines 24-30 and Page 10, lines 1-2:

The present invention further relates to the monoclonal antibody sHIgM46 (LYM46), monomers thereof, active fragments thereof, and natural or synthetic antibodies having the characteristics of sHIgM46. Recombinant antibodies derived from sHIgM46 are further contemplated and are provided herein. The invention provides antibodies comprising a polypeptide having an amino acid sequence corresponding at least in part to a sequence selected from FIGURE 71 (SEQ ID NO: 49) and FIGURE 72 (SEQ ID NO: 51), and active fragments thereof. Recombinant or synthetic antibodies derived or based therefrom and corresponding at least in part to a sequence selected from SEQ ID NO: 49 and 51 are further included in the present invention.

Please substitute the following amended paragraph for the paragraph starting on Page 10, lines 4-15:

The present invention further relates to sequences identified for mouse antibodies suitable and useful in the present invention as neuromodulatory agents having one or more of the following characteristics: they induce remyelination and/or cellular proliferation of glial cells; and/or evoke Ca^{++} signaling with oligodendrocytes. In particular, antibody sequences are provided in FIGURES 67-70. Thus, the neuromodulatory agents of the present invention may

comprise a polypeptide having an amino acid sequence corresponding at least in part, to a sequence selected from the group consisting of FIGURE 67 (SEQ ID NO: 41, 42), FIGURE 68 (SEQ ID NO: 43,44), FIGURE 69 (SEQ ID NO: 45, 46), FIGURE 70 (SEQ ID NO: 47, 48), and active fragments thereof. Recombinant or synthetic antibodies derived or based therefrom and corresponding at least in part to a sequence selected from the above group are further included in the present invention.

Please substitute the following amended paragraph for the paragraph starting on Page 10, lines 29-30, Page 11, lines 1-30 and Page 12, lines 1-14:

More particularly, the recombinant DNA molecule comprises a DNA sequence or degenerate variant thereof, which encodes an antibody, a peptide analog thereof, a hapten corresponding thereto, or an active fragment thereof, and which may be selected from the group consisting of:

(A) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 35 (SEQ ID NO: 8, 7);

(B) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 36 (SEQ ID NO: 10, 9);

(C) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 37 (SEQ ID NO: 11, 12);

(D) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 38 (SEQ ID NO: 13, 14);

(E) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 45 (SEQ ID NO: 15, 16);

(F) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 46 (SEQ ID NO: 17, 18);

(G) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 55 (SEQ ID NO: 25, 26);

(H) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 56 (SEQ ID NO: 27, 28);

(I) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 57 (SEQ ID NO: 29, 30);

(J) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 58 (SEQ ID NO: 31, 32);

(K) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 59 (SEQ ID NO: 33, 34);

(L) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 60 (SEQ ID NO: 35, 36);

(M) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 61 (SEQ ID NO: 37, 38);

(N) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 67 (SEQ ID NO: 41, 42);

(O) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 68 (SEQ ID NO: 43, 44);

(P) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 69 (SEQ ID NO: 45, 46);

(Q) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 70 (SEQ ID NO: 47, 48);

(R) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 71 (SEQ ID NO: 49, 50);

(S) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 72 (SEQ ID NO: 51, 52);

(T) DNA sequences that hybridize to any of the foregoing DNA sequences under standard hybridization conditions; and

(U) DNA sequences that code on expression for an amino acid sequence encoded by any of the foregoing DNA sequences.

Please substitute the following amended paragraph for the paragraph starting on Page 16, lines 28-30, Page 17, lines 1-30 and Page 18, lines 1-11:

More specifically, the therapeutic method generally referred to herein could include the method for the treatment of various pathologies or other cellular dysfunctions and derangements by the administration of pharmaceutical compositions that may comprise effective inhibitors or enhancers of activation of the neuromodulatory agents, or other equally effective drugs developed for instance by a drug screening assay prepared and used in accordance with an aspect of the present invention discussed above. For example, drugs or other binding partners to the neuromodulatory agents or like proteins, having sequences corresponding at least in part to the sequences as represented by FIGURE 35 (SEQ ID NO: 8, 7), FIGURE 36 (SEQ ID NO: 10, 9), FIGURE 37 (SEQ ID NO: 11, 12), FIGURE 38 (SEQ ID NO: 13, 14), FIGURE 45 (SEQ ID NO: 15, 16), FIGURE 46 (SEQ ID NO: 17, 18), FIGURE 55 (SEQ ID NO: 25, 26), FIGURE 56 (SEQ ID NO: 27, 28), FIGURE 57 (SEQ ID NO: 29, 30), FIGURE 58 (SEQ ID NO: 31, 32), FIGURE 59 (SEQ ID NO: 33, 34), FIGURE 60 (SEQ ID NO: 35, 36), FIGURE 61 (SEQ ID NO: 37, 38), FIGURE 71 (SEQ ID NO: 49, 50), FIGURE 72 (SEQ ID NO: 51, 52) may be administered to inhibit or potentiate neuroregeneration, neuroprotection, or remyelination, as in the treatment of Parkinsons disease or multiple sclerosis. In particular, the proteins of one or more antibodies selected from the group of sHIgM22 (LYM22), ebvHIgM MSI19D10, sHIgM46 (LYM46), CB2bG8, AKJR4, CB2iE12, CB2iE7 and MSI19E5, whose sequences are presented in FIGURES 35-38, 45, 46, 55-61, and 71-72, their antibodies, agonists, antagonists, monomers or active fragments thereof, including mixtures and combinations thereof, could be prepared in pharmaceutical formulations including vaccines, for administration in instances wherein neuroregenerative and/or neuroprotective therapy or remyelination is appropriate, such as to treat Alzheimers disease, ALS, Parkinsons disease, or spinal cord injury. The present invention includes combinations or mixtures of the antibodies provided herein, wherein more than one of the antibodies, particularly human antibodies, most particularly selected from the group of sHIgM22, sHIgM46, MSI19E10, CB2bG8, AKJR4, CB2iE12, CB2iE7, MSI19E5, and MSI10E10 can be prepared in pharmaceutical and therapeutic compositions or formulations. Combinations or mixtures of various human antibodies, mouse antibodies, or monomers, fragments, recombinant or synthetic antibodies derived therefrom or based thereon are also provided by and included in the present invention. The human antibodies (extending to

monomers, fragments, recombinant or synthetic antibodies derived therefrom) are particularly selected from the group of sHIgM22, sHIgM46, MSI19E10, CB2bG8, AKJR4, CB2iE12, CB2iE7, MSI19E5, and MSI10E10. The mouse antibodies (extending to monomers, fragments, recombinant or synthetic antibodies and humanized antibodies derived therefrom) are particularly selected from the group of SCH 94.03, SCH79.08, O1, O4, O9, A2B5 and HNK-1. In addition, the invention provides further combinations of the antibody(ies) with therapeutic compounds, drugs or agents useful in any such neuroregenerative and/or neuroprotective therapy or remyelination. For instance, the antibody formulation or composition of the present invention may be combined with therapeutic compounds for the treatment of multiple sclerosis, including but not limited to beta interferon formulations (Betaseron, etc.) and coploymer 1 (Copaxone).

Please substitute the following amended paragraph for the paragraph starting on Page 21, lines 20-22:

FIGURES 11A and 11B show the alignment of the immunoglobulin light (Fig. 11A, SEQ ID NO: 63, 64) and heavy (Fig. 11B, SEQ ID NO: 65, 66) chain variable region sequences of SCH94.03 and control IgM, CH12, and germline Ig gene segments.

Please substitute the following amended paragraph for the paragraph starting on Page 21, lines 24-29 and Page 22, lines 1-2:

FIGURE 12 shows the nucleotide and deduced amino acid sequences of V_H, D and J_H regions encoding O1, compared with the unrearranged V_H segment transcript A1 and A4, and the JH germline gene (SEQ. ID NO: 1, 67). Dashed lines indicate identity with unrearranged V_H segment transcript A1 and A4. Underline indicates identity with germline AP2 gene family (DSP2.3, 2.4, 2.6). Amino acids are represented by the single-letter code. CDR represents the complementarity determining region. This sequence has been assigned the GenBank TM/EMBL Data Bank Accession number L41877.

Please substitute the following amended paragraph for the paragraph starting on Page 22, lines 4-11:

FIGURE 13 shows the nucleotide and deduced amino acid sequences of V_H, D and J_H regions encoding O4 and HNK-1 (SEQ. ID NO: 2, 68), compared with those reported for germline gene V_H101 and J_H, and for natural autoantibody D23. Dashed lines indicate identity with V_H101 and J_H4. Underline indicates identity with germline DFL16.1. Amino acids are represented by the single-letter code. CDR represents the complementarity determining region. These sequences have been assigned the GenBank TM/EMBL Data Bank Accession Numbers L41878 (O4) and L41876 (HNK-a).

Please substitute the following amended paragraph for the paragraph starting on Page 22, lines 13-19:

FIGURE 14 shows the nucleotide and deduced amino acid sequences of V_H, D and J_H regions encoding A2B5 (SEQ. ID NO: 3, 69), compared with those reported for germline gene V1 and J_H3 germline gene. Dashed lines indicate identity with germline gene V1 and J_H3. Underline indicates identity with germline DFL16.2. Amino acids are represented by the single-letter code. CDR represents the complementarity determining region. This sequence has been assigned the GenBank TM/EMBL Data Bank Accession Number L41874.

Please substitute the following amended paragraph for the paragraph starting on Page 22, lines 21-27:

FIGURE 15 shows the nucleotide and deduced amino acid sequences of V_H and J_H regions encoding O1 and O4 (SEQ. ID NO: 4, 70), compared with those reported for myeloma MOPC21, for natural autoantibody E7 and for 3_x2 germline gene. Dashed lines indicate identity with MOPC21 and germline gene J_H2 (N, undetermined nucleotide). Amino acids are represented by the single-letter code. CDR represents the complementarity determining region. These sequence have been assigned the GenBank TM/EMBL Data Bank Accession Numbers L41879 (O1) and L41881 (O4).

Please substitute the following amended paragraph for the paragraph starting on Page 22, lines 29-30 and Page 23, lines 1-4:

FIGURE 16 shows the nucleotide and deduced amino acid sequences of V_H and J_H regions encoding HNK-1 (SEQ. ID NO: 5, 71), compared with those reported for germline V_H41, myeloma MOPC21, and J_H2. Dashed lines indicate identity with germline genes. Amino acids are represented by the single-letter code. CDR represents the complementarity determining region. This sequence has been assigned the GenBank TM/EMBL Data Bank Accession Number L41880.

Please substitute the following amended paragraph for the paragraph starting on Page 23, lines 6-10:

FIGURE 17 shows the nucleotide and deduced amino acid sequences of V_H and J_H regions encoding A2B5 (SEQ. ID NO: 6, 72). Dashed lines indicate identity with germline J_H. Amino acids are represented by the single-letter code. CDR represents the complementarity determining region. This sequence has been assigned the GenBank TM/EMBL Data Bank Accession Number L41875.

Please substitute the following amended paragraph for the paragraph starting on Page 29, lines 29-30 and Page 30, lines 1-12:

FIGURE 35 presents the sHIgM22 heavy chain variable region sequences (SEQ. ID NO: 7, 8). The sequence is aligned according to the numbering system of human V_H sequences in the publication: *Sequences of Proteins of Immunological Interest*, Vol I, Fifth Edition (1991), Kabat E.A., Wu, T.T., Perry, H.M. Gottesman, K.S. and Foeller, C., NIH Publication. The sHIgM22 V_H is a member of the V_H subgroup III. Underlined amino acids have been confirmed by protein sequencing. Amino acid sequence corresponds to sHIgM22 nucleotide sequence. SHIgM22 V_H type A and B sequences are represented only with nucleotides that differ from the IGHV3-30/3-30-05*01, IGHJ4*02 and IGHD2-21*02 germline sequences. Two amino acid replacements in the protein sequence of sHIgM22 V_H type B are printed in bold. The sequences of both SHIgM22 V_H type A and B most closely matched the IGHV3-30/3-30-5*01 germline sequence (96% homology). References for germline sequences: IMGT, the international ImMunoGeneTics database [http://imgt.cnusc.fr:8104]. (Initiator and coordinator: Marie-Paule

Lefranc, Montpellier, France)

Please substitute the following amended paragraph for the paragraph starting on Page 30, lines 14-30:

FIGURE 36 presents the sHIgM22 light chain variable region sequences (SEQ. ID NO: 9, 10). The sequence is aligned according to the numbering system of human V_H sequences in the publication: *Sequences of Proteins of Immunological Interest*, Vol I, Fifth Edition (1991), Kabat E.A., Wu, T.T., Perry, H.M. Gottesman, K.S. and Foeller, C., NIH Publication. V_λ sHIgM22 is a member of the lambda subgroup I. Underlined amino acids have been confirmed by protein sequencing. Amino acid sequence corresponds to sHIgM22 nucleotide sequence. SHIgM22 V_λ type I and II sequences are represented only with nucleotides that differ from the IGLV1-51*01 and IGLJ3*01 germline sequences. Two amino acid replacements in the protein sequence of sHIgM22 V_λ type II are printed in bold. The V_λ sequences from SHIgM22 most closely matched the IGLV-51*01 germline sequence (97% homology). The two genes differ from their common ancestor by a single nucleotide change. References for germline sequences: IMGT, the international ImMunoGeneTics database [http://imgt.cnusc.fr:8104]. (Initiator and coordinator: Marie-Paule Lefranc, Montpellier, France).

Please substitute the following amended paragraph for the paragraph starting on Page 31, line 1:

FIGURE 37 presents the ebvHIgM MSI19D10 heavy chain variable region sequence (SEQ. ID NO: 11, 12).

Please substitute the following amended paragraph for the paragraph starting on Page 31, line 4:

FIGURE 38 presents the ebvHIgM MSI19D10 light chain variable region sequence (SEQ. ID NO: 13, 14).

Please substitute the following amended paragraph for the paragraph starting on Page 34, lines 1-2:

FIGURE 45 presents the heavy chain variable region sequence of EBV transformant antibody CB2b-G8 (SEQ. ID NO: 15, 16).

Please substitute the following amended paragraph for the paragraph starting on Page 34, lines 4-5:

FIGURE 46 presents the light chain variable region sequence of EBV transformant antibody CB2b-G8 (SEQ. ID NO: 17, 18).

Please substitute the following amended paragraph for the paragraph starting on Page 35, lines 19-20:

FIGURE 52 presents the heavy chain variable region sequence of mouse O9 antibody (SEQ. ID NO: 19, 20).

Please substitute the following amended paragraph for the paragraph starting on Page 35, lines 22-23:

FIGURE 53 presents the kappa light chain 1 variable region sequence of mouse O9 variable region sequence of mouse O9 antibody (SEQ. ID NO: 21, 22).

Please substitute the following amended paragraph for the paragraph starting on Page 35, lines 25-26:

FIGURE 54 presents the kappa light chain 2 variable region sequence of mouse O9 antibody (SEQ. ID NO: 23, 24).

Please substitute the following amended paragraph for the paragraph starting on Page 35, line 28:

FIGURE 55 presents the AKJR4 heavy chain variable region sequence (SEQ. ID NO: 25, 26).

Please substitute the following amended paragraph for the paragraph starting on Page 35, line 30:

[redacted]

FIGURE 56 presents the AKJR4 kappa light chain variable region sequence (SEQ. ID NO: 27, 28).

Please substitute the following amended paragraph for the paragraph starting on Page 36, line 1:

FIGURE 57 presents the CB2iE12 heavy chain variable region sequence (SEQ. ID NO: 29, 30).

Please substitute the following amended paragraph for the paragraph starting on Page 36, line 3:

FIGURE 58 presents the CB2iE12 kappa light chain variable region sequence (SEQ. ID NO: 31, 32).

Please substitute the following amended paragraph for the paragraph starting on Page 36, line 5:

FIGURE 59 presents the CB2iE7 heavy chain variable region sequence (SEQ. ID NO: 33, 34).

Please substitute the following amended paragraph for the paragraph starting on Page 36, line 7:

FIGURE 60 presents the CB2iE7 kappa light chain variable region sequence (SEQ. ID NO: 35, 36).

Please substitute the following amended paragraph for the paragraph starting on Page 36, line 9:

FIGURE 61 presents the MSI 19E5 light chain variable region sequence (SEQ. ID NO: 37, 38).

Please substitute the following amended paragraph for the paragraph starting on Page 36, line 11:

FIGURE 62 presents the kappa light chain 2 of the mouse O4 antibody (SEQ. ID NO: 39, 40).

Please substitute the following amended paragraph for the paragraph starting on Page 36, line 27:

FIGURE 67 depicts the kappa light chain sequence of antibody O4 (SEQ. ID NO: 41, 42).

Please substitute the following amended paragraph for the paragraph starting on Page 36, line 29:

FIGURE 68 depicts the kappa light chain sequence of antibody O1 (SEQ. ID NO: 43, 44).

Please substitute the following amended paragraph for the paragraph starting on Page 37, line 1:

FIGURE 69 depicts the kappa light chain sequence of antibody HNK-1 (SEQ. ID NO: 45, 46).

Please substitute the following amended paragraph for the paragraph starting on Page 37, line 3:

FIGURE 70 depicts the kappa light chain sequence of antibody A2B5 (SEQ. ID NO: 47, 48).

Please substitute the following amended paragraph for the paragraph starting on Page 37, line 5:

FIGURE 71 depicts the Lym 46 heavy chain sequence (SEQ. ID NO: 49, 50).

Please substitute the following amended paragraph for the paragraph starting on Page 37, line 7:

FIGURE 72 depicts the Lym 46 kappa light chain sequence (SEQ. ID NO: 51, 52).

Please substitute the following amended paragraph for the paragraph starting on Page 40, lines 11-25:

Also, the terms "neuromodulatory agent," "autoantibody," "antibody peptide," "peptide," "hapten" and any variants not specifically listed, may be used herein interchangeably, to the extent that they may all refer to and include proteinaceous material including single or multiple proteins, and extends to those proteins having the amino acid sequence data described herein and presented in FIGURES 35-38, 45, 46, 55-61 and 71-72 (SEQ ID NOS: 7, 8, 10, 9, 11, 12, 13, 14, 15, 16, 17, 18, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 49 and 51), and the profile of activities set forth herein and in the Claims. Accordingly, proteins displaying substantially equivalent or altered activity are likewise contemplated. These modifications may be deliberate, for example, such as modifications obtained through site-directed mutagenesis, or may be accidental, such as those obtained through mutations in hosts that are producers of the complex or its named subunits. Also, the terms "neuromodulatory agent," "autoantibody," "antibody peptide," "peptide," "hapten" are intended where appropriate, to include within their scope proteins specifically recited herein as well as all substantially homologous analogs and allelic variations.

Please substitute the following amended paragraph for the paragraph starting on Page 46, lines 8-16:

It should be appreciated that also within the scope of the present invention are DNA sequences encoding an antibody of the invention, or a peptide analog, hapten, or active fragment thereof, which code for a peptide that defines in at least a portion thereof, or has the same amino acid sequence as set forth in FIGURES 35-38, 45, 46, 55-61 and 71-72 (SEQ ID NOS: 7, 8, 10, 9, 11, 12, 13, 14, 15, 16, 17, 18, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 49 and 51), but which are degenerate to the same SEQ ID NOS. By "degenerate to" is meant that a different three-letter codon is used to specify a particular amino acid. It is well known in the art that the following codons can be used interchangeably to code for each specific amino acid:

Please substitute the following amended paragraph for the paragraph starting on Page 185, lines 18-29:

The structures of the IgM heavy and light chains for both the antibodies derived from the EBV-transformants have been determined by analysis of cDNA generated from immunoglobulin mRNA isolated from the cells. The sequences of the heavy and light chain variable regions of MSI 19-D10 and sHIgM22 are provided in **Figures 35-38** (SEQ ID NOS: 11, 12, 13, 14 and 7, 8, 9 and 10). The sequences of the heavy and light chain variable regions of CB2b-G8 are provided in **Figures 45 and 46** (SEQ ID NOS: 15, 16, 17, 18). The sequences themselves are not remarkable other than they differ somewhat from known germline immunoglobulin sequences. Thus, they may be the products of somatic diversification during the course of immune responses against unidentified antigens. The value of the sequences is that they provide a blue print for the construction of expression vectors for the production of the immunoglobulin under controlled conditions.

Please substitute the following amended paragraph for the paragraph starting on Page 185, lines 31-33 and Page 186, lines 1-14:

Similarly, the structures of the heavy and light chains from the serum of one of the IgM-producing patients were determined by protein sequence analysis, followed by cloning and sequence analysis of cDNA from peripheral blood mononuclear cells isolated from the patient. Two closely related heavy and light chains were identified in the patient's serum, designated sHIgM22 (**Figures 35** and **36**) (SEQ ID NOS: 7, 8, 9, 10). The two heavy and two light chains were both present in the isolated cDNA populations at a ration of 60:40. Both antibodies share a common μ-VDJ rearrangement and λ-VJ rearrangement, indicting that they are derived from a common B cell precursor. They have subsequently diverged, as a result of the accumulation of mutations that have altered the structures of their variable regions. We conclude that both antibodies are expressed in the serum of the patient because peptides from both antibodies were characterized from the protein isolated from the serum. However, the two distinct combinations of variable and light chains were not observed directly, leaving open the possibility that other combinations of the identified heavy and light chains may actually be present. Based on the

positions of the observed amino acid substitutions, we suspect that the antibodies have very similar reactivity patterns.

Please substitute the following amended paragraph for the paragraph starting on Page 188, lines 14-21:

The heavy chain variable region of the mouse IgM monoclonal antibody 94.03 was isolated from cDNA by PCR using the RsrII primer ACTCCCAAGTCGGCTCGCTTTCTCTTCAGTGACAAACACAGACATAGAACATTCACC ATGGGATGGAGCTGTATCACT (SEQ ID NO: 53) to introduce the RsrII site upstream of the leader sequence and the PacI primer ACTGACTCTCTTAATTAAGACTCACCTGAGGAGACTGTGAGAGTGGT (SEQ ID NO: 54) to introduce the PacI site while maintaining the correct splice junction at the 3' end of the variable region coding block.

Please substitute the following amended paragraph for the paragraph starting on Page 189, lines 7-16:

The chimeric light chain gene was assembled from two cDNA sequences using the PCR splicing by overlap extension technique (Horton et al. Gene 77:61:1989). The primers flanking the fused regions of the chimeric cDNA (contained the enzyme recognition sequences for the endonuclease Xho I and Nhe I. The 5' primer used to amplify the fused gene product was TTGGCGCGCCAAAGACTCAGCCTGGACATGATGTCCTCTGCTCAGTTC (SEQ ID NO: 55) ; the 3' primer was ATAGTTTAGCGGCCGCATTCTTATCTAACACTCTCCCCTGTTG (SEQ ID NO: 56). The cDNA coding block was inserted into the light chain cassette vector using these sites.

Please substitute the following amended paragraph for the paragraph starting on Page 190, lines 1-15:

Insertion of sHIgM22 sequences into the expression vector system

The cDNA of mRNA encoding the heavy and light chains of sHIgM22 were prepared by PCR

amplification of peripheral blood RNA using 5' primers deduced from amino acid sequence information and sequences in the constant regions of the heavy and light chain respectively. The heavy chain variable region coding block, leader sequence and donor splice junction along with the flanking RsrII and Pac I sites were assembled by using PCR to add the 5' region GACTCGGTCCGCCCAGCCACTGGAAGTCGCCGGTGTTTCCATTCGGTGATCATCACT GAACACAGAGGACTCACCATGGAGTTTGGGCTGAGCTGGGTTTTCCTCGTTGCTCTT TTAAGAGGTGTCCAGTGTCAGGTGCAGCTGGTGGAGTCTGG (SEQ ID NO: 57) and the 3' sequences CCTTAATTAAGACCTGGAGAGGCCATTCTTACCTGAGGAGACGGTGACCAGGGTTC (SEQ ID NO: 58). The resulting DNA molecule was digested with Rsr II and Pac I and subsequently cloned into the expression vector, substituting the desired variable region sequence for the irrelevant sequence in the vector.

Please substitute the following amended paragraph for the paragraph starting on Page 190, lines 17-22:

The light chain sequence was assembled in two steps. The lambda constant region was isolated from mRNA by RT-PCR using the 5' primer CTAGCTAGCGTCCTAGGTCAGCCCAAGGCTGCCCCC (SEQ ID NO: 59) and 3' primer ATAGTTTAGCGGCCGCACCTATGAACATTCTGTAGG (SEQ ID NO: 60). This fragment was cloned using a unique AvrII site and a 3' Not I site into the pCIneo vector.

Please substitute the following amended paragraph for the paragraph starting on Page 190, lines 24-30 and Page 191, lines 1-5:

The variable region of sHIgM22 was generated by RT-PCR using the 5' primer CTAGCTAGCCCGAATTTCGGGACAATCTTCATCATGACCTGCTCCCCTCTCCTCCTCA CCCTTCTCATTCACTGCACAGGGTCCTGGGCCCAGTCTGTGTTGACGCAGCCG (SEQ ID NO: 61) in order to introduce the needed Nhe I site and leader sequence onto the cDNA. The 3' primer, GGGCAGCCTTGGGCTGAGCTAGGACGGTCAGC (SEQ ID NO: 62), was used to introduce an AvrII site so that this fragment could be joined with the constant region piece. The

resulting coding block containing a functional leader signal was flanked by the necessary NheI and Xho I sites for cloning into the dHFR/light chain cassette, which was subsequently assembled with the heavy chain plasmid to generate the final product containing both the heavy and light chain coding sequences and promoters needed for expression in mammalian cells.

Please substitute the following amended paragraph for the paragraph starting on Page 191, lines 25-30 and Page 192, lines 1-6:

EXAMPLE 11

IgG_3 ISOTYPE ANTI-OLIGODENDROCYTE MOUSE ANTIBODY O9

The mouse O9 antibody was isolated as an anti-oligodendrocyte antibody and is of the IgG_3 subtype (Kuhlmann-Krieg, S., Sammer, I. and Shachner M. (1988) *Devel Brain Res* **39**:269-280). The O9 antibody binds strongly and specifically to white matter in the CNS. We examined and demonstrated the ability of the O9 antibody to stimulate remyelination in the TMEV model. The O9 antibody heavy chain variable region sequence is provided in **Figure 52** (SEQ ID NOS: 19 and 20). The sequence of the kappa light chain 1 variable region of O9 is provided in **Figure 53** (SEQ ID NOS: 21 and 22). The sequence of the kappa light chain 2 variable region of O9 is provided in **Figure 54** (SEQ ID NOS: 23 and 24).

Please substitute the following amended paragraph for the paragraph starting on Page 196, lines 24-33:

EXAMPLE 14

The sequences of the heavy and light chain variable regions of human antibodies AKJR4, CB2iE12 and CB2iE7, and the light chain variable region of MSI19E5 were determined. The sequences of the heavy and light chain variable region of AKJR4 are shown in **Figures 55** and **56** respectively (SEQ ID NOS: 25, 26, 27, 28). The sequences of the heavy and light chain variable region of CB2iE12 are shown in **Figures 57** and **58**, respectively (SEQ ID NOS: 29, 30, 31, 32). The sequences of the heavy and light chain variable region of CB2iE7 are shown in **Figures 59** and **60**, respectively (SEQ ID NOS: 33, 34, 35, 36). The sequence of the light chain variable region of MSI19E5 is shown in **Figure 61**, respectively (SEQ ID NOS: 37, 38).

Please substitute the following amended paragraph for the paragraph starting on Page 203, lines 19-26:

O9 kappa chain sequence:

O9 hybridoma produces two light chains. One of them (noted above and in **FIGURE 53** (SEQ ID NOS: 21, 22) as "O9 kappa light chain 1") is ubiquitous for all O-series hybridomas and originates from MOPC21 fusion partner. This light chain does not appear to be important for the antibody activity of interest. The sequence of the O9-characteristic kappa chain (noted as "O9 kappa light chain 2" and provided in **FIGURE 54** (SEQ ID NOS: 23, 24) remains unchanged and is the correct O9 kappa chain sequence.

Please substitute the following amended paragraph for the paragraph starting on Page 203, lines 28-30:

O4 kappa chain sequence:

The correct and complete O4 kappa chain sequence is shown in **FIGURE 67** (SEQ ID NOS: 41, 42).

Please substitute the following amended paragraph for the paragraph starting on Page 204, lines 3-6:

O1 kappa chain sequence:

This sequence, provided in **FIGURE 68** (SEQ ID NOS: 43, 44) is completely new. The previously reported O1 kappa chain was the shared MOPC21 kappa chain which is also produced by the O1 hybridoma.

Please substitute the following amended paragraph for the paragraph starting on Page 204, lines 8-12:

HNK-1 kappa chain sequence:

The published HNK-1 sequence and the newly obtained sequence differ in two nucleotides: 174 (G-C) and 281 (C-T, this changes the amino acid from S to F). The changes are highlighted on the sequence provided in **FIGURE 69** (SEQ ID NOS: 45, 46).

Please substitute the following amended paragraph for the paragraph starting on Page 204, lines 14-17:

A2B5 kappa chain sequence:

This sequence of A2B5 kappa chain shown in **FIGURE 70** (SEQ ID NOS: 47, 48) is completely new. The previously reported A2B5 kappa chain sequence is in fact the O4 kappa chain sequence.

Please substitute the following amended paragraph for the paragraph starting on Page 204, lines 23-26:

The sequence of LYM46 was determined. The amino acid sequence (SEQ ID NO: 49) and nucleic acid sequence (SEQ ID NO: 50) of the LYM46 heavy chain are depicted in FIGURE 71. The amino acid sequence (SEQ ID NO: 51) and nucleic acid sequence (SEQ ID NO: 52) of the LYM46 heavy chain are depicted in FIGURE 72.

Please substitute the following amended paragraph for the paragraph starting on Page 205, lines 21-23:

The Lym 46 heavy chain variable region sequence was synthesized using overlapping oligonucleotides and cloned into pUDM. The oligonucleotides used were:
5' act ccc aag tcg gtc cgc ttt (SEQ. ID NO: 73).

Please substitute the following amended paragraph for the paragraph starting on Page 205, lines 25-30 and Page 206, line 1:

Template A-- act ccc aag tcg gtc cgc ttt ctc ttc agt gac aaa cac aga cat aga aca ttc acc ATG GAG TTT GGG CTG ACC TGG CTT TCT CTT GTT GCT ATT TTA GAA GGT GTC CAG TGT GAG GTG CAG CTG GTG GAG TCT GGG GGA GGC TTG GTC CAG CCT GGG GGG TCC CTG AGA CTC TCC TGT GCA GCC TCT GGA TTC ACC TTT AGT AGC TAT TGG ATG ACC TGG GTC CGC CAG GCT CCA GGG (SEQ. ID NO: 74)

Please substitute the following amended paragraph for the paragraph starting on Page

206, lines 3-8:

Template B -- CTG GAG TGG GTG GCC AAC ATA AAG AAA GAT GGA AGT GAG AAA TCC TAT GTG GAC TCT GTG AAG GGC CGA TTC ACC ACC TCC AGA GAC AAC GCC AAG AAC TCA CTG TAT CTG CAA ATG AAC AGC CTG AGA GCC GAG GAC ACG GCT GTG TAT TAC TGT GCG AGA CCC AAT TGT GGT GGT GAC TGC TAT TTA CCA TGG TAC TTC GAT CTC TGG GGC CGT GGC ACC CTG GTC ACT GTC TCC TCA ggt gag tct taa tta aga gag tca gt (SEQ. ID NO: 75)

Please substitute the following amended paragraph for the paragraph starting on Page 206, line 10:

3' primer -- act gac tct ctt aat tag (SEQ. ID NO: 76)

Please substitute the following amended paragraph for the paragraph starting on Page 206, lines 19-21:

5' primer containing the leader sequence CTA GCT AGC TCA AGA CTC AGC CTG GAC ATG GTG TTG CAG ACC CAG GTC TTC ATT TCT CTG TTG CTC TGG ATC TCT GGT GCC TAC GGG GAC ATC GTG ATG ACC CAG (SEQ. ID NO: 77)

Please substitute the following amended paragraph for the paragraph starting on Page 206, line 23:

3' primer GAA CGC CTG AGG AGT ATT AT (SEQ. ID NO: 78)

Please substitute the following amended paragraph for the paragraph starting on Page 207, lines 12-13, please amend the description as follows:

5 ' Primer for all human IgG subclasses with Bam HI site:
CTG ATG CTA CGA TGG ATC C GC CTC CAC CAA GGG CCC ATC (SEQ. ID NO: 79)

Please substitute the following amended paragraph for the paragraph starting on Page 207, lines 15-16:

3' Primer for gamma 1, and 2 with Sal 1 site:
GCA TGA GTC TGA CAG CTG TTT ACC CGG AGA CAG GGA GAG GCT (SEQ. ID NO: 80)

IN THE CLAIMS:

Please substitute the following amended claims for the claims having the same claim number:

6. (Amended) The method of Claim 5 wherein the light chain of said SHIgM22 (LYM22) comprises the amino acid sequence selected from SEQ ID NOS: 10 and 9.

7. (Amended) The method of Claim 5 wherein the heavy chain of said SHIgM22 (LYM22) comprises the amino acid sequence selected from SEQ ID NOS: 8 and 7.

9. (Amended) The method of Claim 8 wherein the light chain of said sHIgM46 (LYM46) comprises the amino acid sequence selected from SEQ ID NO: 51.

10. (Amended) The method of Claim 8 wherein the heavy chain of said sHIgM46(LYM46) comprises the amino acid sequence selected from SEQ ID NO: 49.

40. (Amended) A method according to any of Claims 5, 8, 15, 16, 23, 24, 32, 33, 38 or 39 wherein said monoclonal antibody has an amino acid sequence which corresponds at least in part to an amino acid sequence selected from the group consisting of FIGURE 35 (SEQ ID NO: 8, 7), FIGURE 36 (SEQ ID NO: 10, 9), FIGURE 71 (SEQ ID NO: 49), FIGURE 72 (SEQ ID NO: 51) and active fragments thereof.

45. (Amended) A DNA sequence or degenerate variant thereof, which encodes an antibody, a peptide analog thereof, a hapten corresponding thereto, or an active fragment thereof, selected from the group consisting of:

(A) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 35 (SEQ ID NO: 8, 7);

(B) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 36 (SEQ ID NO: 10, 9);

(C) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 71 (SEQ ID NO: 49);

(D) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 72 (SEQ ID NO: 51);

(E) DNA sequences that hybridize to any of the foregoing DNA sequences under standard hybridization conditions; and

(F) DNA sequences that code on expression for an amino acid sequence encoded by any of the foregoing DNA sequences.

46. (Amended) A recombinant DNA molecule comprising a DNA sequence or degenerate variant thereof, which encodes an antibody, a peptide analog thereof, a hapten corresponding thereto, or an active fragment thereof, selected from the group consisting of:

(A) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 35 (SEQ ID NO: 8, 7);

(B) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 36 (SEQ ID NO: 10, 9);

(C) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 71 (SEQ ID NO: 49);

(D) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 72 (SEQ ID NO: 51);

(E) DNA sequences that hybridize to any of the foregoing DNA sequences under standard hybridization conditions; and

(F) DNA sequences that code on expression for an amino acid sequence encoded by any of the foregoing DNA sequences.

50. (Amended) A unicellular host transformed with a recombinant DNA molecule comprising a DNA sequence or degenerate variant thereof, which encodes an antibody, a peptide analog thereof, a hapten corresponding thereto, or an active fragment thereof, said DNA sequence selected from the group consisting of:

(A) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 35 (SEQ ID NO: 8, 7);

(B) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 36 (SEQ ID NO: 10, 9);

(C) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 71 (SEQ ID NO: 49);

(D) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 72 (SEQ ID NO: 51);

(E) DNA sequences that hybridize to any of the foregoing DNA sequences under standard hybridization conditions; and

(F) DNA sequences that code on expression for an amino acid sequence encoded by any of the foregoing DNA sequences;

wherein said DNA sequence is operatively linked to an expression control sequence.

58. (Amended) The method of Claim 57 wherein said autoantibody has an amino acid sequence which corresponds at least in part to an amino acid sequence selected from the group consisting of FIGURE 35 (SEQ ID NO: 8, 7), FIGURE 36 (SEQ ID NO: 10, 9), FIGURE 71 (SEQ ID NO: 49), FIGURE 72 (SEQ ID NO: 51) and active fragments thereof.

62. (Amended) An antibody produced by injecting a substantially immunocompetent host with an antibody-producing effective amount of an antibody peptide, and harvesting said antibody, said antibody peptide comprising an amino acid sequence selected from the group consisting of FIGURE 35 (SEQ ID NO: 8, 7), FIGURE 36 (SEQ ID NO: 10, 9), FIGURE 71 (SEQ ID NO: 49), FIGURE 72 (SEQ ID NO: 51) and active fragments thereof.

REMARKS

The specification has been amended to insert corrected sequence identifiers in compliance with the requirements of 37 CFR 1.821-1.825. A paper and electronic copy of the Sequence Listing has been mailed to a separate address. A paper copy is included herewith for the Examiner's reference and instructions are contained herein for the insertion of the Sequence Listing into the specification at the end of the Abstract.

In view of the above and foregoing, completion of the filing of the present application and an early and favorable action on the merits are believed to be in order and are courteously solicited.

Respectfully submitted,

DAVID A. JACKSON
Attorney for Applicant(s)
Registration No. 26,742

KLAUBER & JACKSON
411 Hackensack Avenue
Hackensack, NJ 07601
(201) 487-5800

Enclosure

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The paragraph starting on Page 8, lines 18-30 and Page 9, lines 1-11 has been amended as follows:

More particularly, the antibodies comprehended within the scope of neuromodulatory agents of the invention may be selected from the group consisting of mAb SCH94.03, SCH79.08, O1, O4, O9, A2B5, HNK-1, sHIgM22 (LYM 22), ebvHIgM MSI19D10, sHIgM46 (LYM46), CB2bG8, AKJR4, CB2iE12, CB2iE7, MSI19E5, MSI10E10, mixtures thereof, monomers thereof, active fragments thereof, and natural or synthetic autoantibodies having the characteristics of the particular mAb SCH94.03, SCH79.08, O1, O4, O9, A2B5, HNK-1, sHIgM22 (LYM 22), ebvHIgM MSI19D10,sHIgM46 (LYM46), CB2bG8, AKJR4, CB2iE12, CB2iE7, MSI19E5 and MSI10E10. Antibodies further comprehended within the scope of the neuromodulatory agents of the invention are recombinant antibodies derived from mAb SCH94.03, SCH79.08, O1, O4, O9, A2B5, HNK-1, sHIgM22 (LYM 22), ebvHIgM MSI19D10, sHIgM46 (LYM46), CB2bG8, AKJR4, CB2iE12, CB2iE7, and MSI10E10. The present neuromodulatory agents may be derived from mammalian cells and specifically, may be derived from human cells. Further, the neuromodulatory agents may comprise a polypeptide having an amino acid sequence corresponding at least in part, to a sequence selected from the group consisting of FIGURE 35 (SEQ ID NO: [38] 8, [86] 7), FIGURE 36 (SEQ ID NO: [42] 10, [87] 9), FIGURE 37 (SEQ ID NO:[46] 11, 12), FIGURE 38 (SEQ ID NO:[48] 13, 14), FIGURE 45 (SEQ ID NO:[50] 15, 16), FIGURE 46 (SEQ ID NO: [52] 17, 18), FIGURE 55 (SEQ ID NO: [60] 25, 26), FIGURE 56 (SEQ ID NO:[62] 27, 28), FIGURE 57 (SEQ ID NO: [64] 29, 30), FIGURE 58 (SEQ ID NO:[66] 31, 32), FIGURE 59 (SEQ ID NO: [68] 33, 34), FIGURE 60 (SEQ ID NO: [70] 35, 36), FIGURE 61 (SEQ ID NO: [72] 37, 38), FIGURE 71 (SEQ ID NO:[96] 49), FIGURE 72 (SEQ ID NO:[98] 51) and active fragments thereof. Recombinant or synthetic antibodies derived or based therefrom and corresponding at least in part to a sequence selected from the above group are further included in the present invention.

The paragraph starting on Page 9, lines 13-22 has been amended as follows:

The present invention thus relates to the monoclonal antibody sHIgM22 (LYM22), monomers thereof, active fragments thereof, and natural or synthetic antibodies having the characteristics of sHIgM22. Recombinant antibodies derived from sHIgM22 are further contemplated and are provided herein. The invention provides antibodies comprising a polypeptide having an amino acid sequence corresponding at least in part to a sequence selected from FIGURE 35 (SEQ ID NO: [38] 8, [86] 7) and FIGURE 36 (SEQ ID NO: [42] 10, [87] 9), and active fragments thereof. Recombinant or synthetic antibodies derived or based therefrom and corresponding at least in part to a sequence selected from SEQ ID NO:[38] 8, [86] 7, [42] 10 and [87] 9 are further included in the present invention.

The paragraph starting on Page 9, lines 24-30 and Page 10, lines 1-2 has been amended as follows:

The present invention further relates to the monoclonal antibody sHIgM46 (LYM46), monomers thereof, active fragments thereof, and natural or synthetic antibodies having the characteristics of sHIgM46. Recombinant antibodies derived from sHIgM46 are further contemplated and are provided herein. The invention provides antibodies comprising a polypeptide having an amino acid sequence corresponding at least in part to a sequence selected from FIGURE 71 (SEQ ID NO:[96] 49) and FIGURE 72 (SEQ ID NO: [98] 51), and active fragments thereof. Recombinant or synthetic antibodies derived or based therefrom and corresponding at least in part to a sequence selected from SEQ ID NO: [96] 49 and [98] 51 are further included in the present invention.

The paragraph starting on Page 10, lines 4-15 has been amended as follows:

The present invention further relates to sequences identified for mouse antibodies suitable and useful in the present invention as neuromodulatory agents having one or more of the following characteristics: they induce remyelination and/or cellular proliferation of glial cells; and/or evoke Ca^{++} signaling with oligodendrocytes. In particular, antibody sequences are provided in FIGURES 67-70. Thus, the neuromodulatory agents of the present invention may

comprise a polypeptide having an amino acid sequence corresponding at least in part, to a sequence selected from the group consisting of FIGURE 67 (SEQ ID NO: [88] 41, 42), FIGURE 68 (SEQ ID NO:[90] 43,44), FIGURE 69 (SEQ ID NO:[92] 45, 46), FIGURE 70 (SEQ ID NO: [94] 47, 48), and active fragments thereof. Recombinant or synthetic antibodies derived or based therefrom and corresponding at least in part to a sequence selected from the above group are further included in the present invention.

The paragraph starting on Page 10, lines 29-30, Page 11, lines 1-30 and Page 12, lines 1-14 has been amended as follows:

More particularly, the recombinant DNA molecule comprises a DNA sequence or degenerate variant thereof, which encodes an antibody, a peptide analog thereof, a hapten corresponding thereto, or an active fragment thereof, and which may be selected from the group consisting of:

(A) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 35 (SEQ ID NO:[38] 8,[86] 7);

(B) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 36 (SEQ ID NO:[42] 10,[87] 9);

(C) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 37 (SEQ ID NO:[46] 11, 12);

(D) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 38 (SEQ ID NO:[48] 13, 14);

(E) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 45 (SEQ ID NO:[50] 15, 16);

(F) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 46 (SEQ ID NO:[52] 17, 18);

(G) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 55 (SEQ ID NO:[60] 25, 26);

(H) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 56 (SEQ ID NO:[62] 27, 28);

(I) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 57 (SEQ ID NO:[64] 29, 30);

(J) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 58 (SEQ ID NO:[66] 31, 32);

(K) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 59 (SEQ ID NO:[68] 33, 34);

(L) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 60 (SEQ ID NO:[70] 35, 36);

(M) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 61 (SEQ ID NO:[72] 37, 38);

(N) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 67 (SEQ ID NO:[88] 41, 42);

(O) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 68 (SEQ ID NO:[90] 43, 44);

(P) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 69 (SEQ ID NO:[92] 45, 46);

(Q) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 70 (SEQ ID NO:[94] 47, 48);

(R) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 71 (SEQ ID NO:[96] 49, 50);

(S) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 72 (SEQ ID NO:[98] 51, 52);

(T) DNA sequences that hybridize to any of the foregoing DNA sequences under standard hybridization conditions; and

(U) DNA sequences that code on expression for an amino acid sequence encoded by any of the foregoing DNA sequences.

The paragraph starting on Page 16, lines 28-30, Page 17, lines 1-30 and Page 18, lines 1-11 has been amended as follows:

More specifically, the therapeutic method generally referred to herein could include the method for the treatment of various pathologies or other cellular dysfunctions and derangements by the administration of pharmaceutical compositions that may comprise effective inhibitors or enhancers of activation of the neuromodulatory agents, or other equally effective drugs developed for instance by a drug screening assay prepared and used in accordance with an aspect of the present invention discussed above. For example, drugs or other binding partners to the neuromodulatory agents or like proteins, having sequences corresponding at least in part to the sequences as represented by FIGURE 35 (SEQ ID NO:[38] 8,[86] 7), FIGURE 36 (SEQ ID NO:[42] 10, [87] 9), FIGURE 37 (SEQ ID NO:[46] 11, 12), FIGURE 38 (SEQ ID NO:[48] 13, 14), FIGURE 45 (SEQ ID NO:[50] 15, 16), FIGURE 46 (SEQ ID NO:[52] 17, 18), FIGURE 55 (SEQ ID NO:[60] 25, 26), FIGURE 56 (SEQ ID NO:[62] 27, 28), FIGURE 57 (SEQ ID NO:[64] 29, 30), FIGURE 58 (SEQ ID NO:[66] 31, 32), FIGURE 59 (SEQ ID NO:[68] 33, 34), FIGURE 60 (SEQ ID NO:[70] 35, 36), FIGURE 61 (SEQ ID NO:[72] 37, 38), FIGURE 71 (SEQ ID NO: [96] 49, 50), FIGURE 72 (SEQ ID NO:[98] 51, 52) may be administered to inhibit or potentiate neuroregeneration, neuroprotection, or remyelination, as in the treatment of Parkinsons disease or multiple sclerosis. In particular, the proteins of one or more antibodies selected from the group of sHIgM22 (LYM22), ebvHIgM MSI19D10, sHIgM46 (LYM46), CB2bG8, AKJR4, CB2iE12, CB2iE7 and MSI19E5, whose sequences are presented in FIGURES 35-38, 45, 46, 55-61, and 71-72, their antibodies, agonists, antagonists, monomers or active fragments thereof, including mixtures and combinations thereof, could be prepared in pharmaceutical formulations including vaccines, for administration in instances wherein neuroregenerative and/or neuroprotective therapy or remyelination is appropriate, such as to treat Alzheimers disease, ALS, Parkinsons disease, or spinal cord injury. The present invention includes combinations or mixtures of the antibodies provided herein, wherein more than one of the antibodies, particularly human antibodies, most particularly selected from the group of sHIgM22, sHIgM46, MSI19E10, CB2bG8, AKJR4, CB2iE12, CB2iE7, MSI19E5, and MSI10E10 can be prepared in pharmaceutical and therapeutic compositions or formulations. Combinations or mixtures of various human antibodies, mouse antibodies, or monomers, fragments, recombinant or synthetic antibodies derived therefrom or based thereon are also provided by and included in the present

invention. The human antibodies (extending to monomers, fragments, recombinant or synthetic antibodies derived therefrom) are particularly selected from the group of sHIgM22, sHIgM46, MSI19E10, CB2bG8, AKJR4, CB2iE12, CB2iE7, MSI19E5, and MSI10E10. The mouse antibodies (extending to monomers, fragments, recombinant or synthetic antibodies and humanized antibodies derived therefrom) are particularly selected from the group of SCH 94.03, SCH79.08, O1, O4, O9, A2B5 and HNK-1. In addition, the invention provides further combinations of the antibody(ies) with therapeutic compounds, drugs or agents useful in any such neuroregenerative and/or neuroprotective therapy or remyelination. For instance, the antibody formulation or composition of the present invention may be combined with therapeutic compounds for the treatment of multiple sclerosis, including but not limited to beta interferon formulations (Betaseron, etc.) and coploymer 1 (Copaxone).

The paragraph starting on Page 21, lines 20-22 has been amended as follows:

FIGURES 11A and 11B show the alignment of the immunoglobulin light (Fig. 11A, SEQ ID NO: 63, 64) and heavy (Fig. 11B, SEQ ID NO: 65, 66) chain variable region sequences of SCH94.03 and control IgM, CH12, and germline Ig gene segments.

The paragraph starting on Page 21, lines 24-29 and Page 22, lines 1-2 has been amended as follows:

FIGURE 12 shows the nucleotide and deduced amino acid sequences of V_H, D and J_H regions encoding O1, compared with the unrearranged V_H segment transcript A1 and A4, and the JH germline gene (SEQ. ID NO: 1, 67). Dashed lines indicate identity with unrearranged V_H segment transcript A1 and A4. Underline indicates identity with germline AP2 gene family (DSP2.3, 2.4, 2.6). Amino acids are represented by the single-letter code. CDR represents the complementarity determining region. This sequence has been assigned the GenBank TM/EMBL Data Bank Accession number L41877.

The paragraph starting on Page 22, lines 4-11 has been amended as follows:

FIGURE 13 shows the nucleotide and deduced amino acid sequences of V_H, D and J_H regions encoding O4 and HNK-1 (SEQ. ID NO: 2, 68), compared with those reported for germline gene V_H101 and J_H, and for natural autoantibody D23. Dashed lines indicate identity with V_H101 and J_H4. Underline indicates identity with germline DFL16.1. Amino acids are represented by the single-letter code. CDR represents the complementarity determining region. These sequences have been assigned the GenBank TM/EMBL Data Bank Accession Numbers L41878 (O4) and L41876 (HNK-a).

The paragraph starting on Page 22, lines 13-19 has been amended as follows:

FIGURE 14 shows the nucleotide and deduced amino acid sequences of V_H, D and J_H regions encoding A2B5 (SEQ. ID NO: 3, 69), compared with those reported for germline gene V1 and J_H3 germline gene. Dashed lines indicate identity with germline gene V1 and J_H3. Underline indicates identity with germline DFL16.2. Amino acids are represented by the single-letter code. CDR represents the complementarity determining region. This sequence has been assigned the GenBank TM/EMBL Data Bank Accession Number L41874.

The paragraph starting on Page 22, lines 21-27 has been amended as follows:

FIGURE 15 shows the nucleotide and deduced amino acid sequences of V_H and J_H regions encoding O1 and O4 (SEQ. ID NO: 4, 70), compared with those reported for myeloma MOPC21, for natural autoantibody E7 and for 3_x2 germline gene. Dashed lines indicate identity with MOPC21 and germline gene J_H2 (N, undetermined nucleotide). Amino acids are represented by the single-letter code. CDR represents the complementarity determining region. These sequence have been assigned the GenBank TM/EMBL Data Bank Accession Numbers L41879 (O1) and L41881 (O4).

The paragraph starting on Page 22, lines 29-30 and Page 23, lines 1-4 has been amended as follows:

FIGURE 16 shows the nucleotide and deduced amino acid sequences of V_H and J_H regions encoding HNK-1 (SEQ. ID NO: 5,71), compared with those reported for germline V_H41, myeloma MOPC21, and J_H2. Dashed lines indicate identity with germline genes. Amino acids are represented by the single-letter code. CDR represents the complementarity determining region. This sequence has been assigned the GenBank TM/EMBL Data Bank Accession Number L41880.

The paragraph starting on Page 23, lines 6-10 has been amended as follows:

FIGURE 17 shows the nucleotide and deduced amino acid sequences of V_H and J_H regions encoding A2B5 (SEQ. ID NO: 6, 72). Dashed lines indicate identity with germline J_H. Amino acids are represented by the single-letter code. CDR represents the complementarity determining region. This sequence has been assigned the GenBank TM/EMBL Data Bank Accession Number L41875.

The paragraph starting on Page 29, lines 29-30 and Page 30, lines 1-12 has been amended as follows:

FIGURE 35 presents the sHIgM22 heavy chain variable region sequences (SEQ. ID NO: 7, 8). The sequence is aligned according to the numbering system of human V_H sequences in the publication: *Sequences of Proteins of Immunological Interest*, Vol I, Fifth Edition (1991), Kabat E.A., Wu, T.T., Perry, H.M. Gottesman, K.S. and Foeller, C., NIH Publication. The sHIgM22 V_H is a member of the V_H subgroup III. Underlined amino acids have been confirmed by protein sequencing. Amino acid sequence corresponds to sHIgM22 nucleotide sequence. SHIgM22 V_H type A and B sequences are represented only with nucleotides that differ from the IGHV3-30/3-30-05*01, IGHJ4*02 and IGHD2-21*02 germline sequences. Two amino acid replacements in the protein sequence of sHIgM22 V_H type B are printed in bold. The sequences of both SHIgM22 V_H type A and B most closely matched the IGHV3-30/3-30-5*01 germline sequence (96% homology). References for germline sequences: IMGT, the international

ImMunoGeneTics database [http://imgt.cnusc.fr:8104]. (Initiator and coordinator: Marie-Paule Lefranc, Montpellier, France)

The paragraph starting on Page 30, lines 14-30 has been amended as follows:

FIGURE 36 presents the sHIgM22 light chain variable region sequences. (SEQ. ID NO: 9, 10) The sequence is aligned according to the numbering system of human V_H sequences in the publication: *Sequences of Proteins of Immunological Interest*, Vol I, Fifth Edition (1991), Kabat E.A., Wu, T.T., Perry, H.M. Gottesman, K.S. and Foeller, C., NIH Publication. V_λ sHIgM22 is a member of the lambda subgroup I. Underlined amino acids have been confirmed by protein sequencing. Amino acid sequence corresponds to sHIgM22 nucleotide sequence. SHIgM22 V_λ type I and II sequences are represented only with nucleotides that differ from the IGLV1-51*01 and IGLJ3*01 germline sequences. Two amino acid replacements in the protein sequence of sHIgM22 V_λ type II are printed in bold. The V_λ sequences from SHIgM22 most closely matched the IGLV-51*01 germline sequence (97% homology). The two genes differ from their common ancestor by a single nucleotide change. References for germline sequences: IMGT, the international ImMunoGeneTics database [http://imgt.cnusc.fr:8104]. (Initiator and coordinator: Marie-Paule Lefranc, Montpellier, France).

The paragraph starting on Page 31, line 1 has been amended as follows:

FIGURE 37 presents the ebvHIgM MSI19D10 heavy chain variable region sequence (SEQ. ID NO: 11, 12).

The paragraph starting on Page 31, line 4 has been amended as follows:

FIGURE 38 presents the ebvHIgM MSI19D10 light chain variable region sequence (SEQ. ID NO: 13, 14).

The paragraph starting on Page 34, lines 1-2 has been amended as follows:

FIGURE 45 presents the heavy chain variable region sequence of EBV transformant antibody CB2b-G8 (SEQ. ID NO: 15, 16).

The paragraph starting on Page 34, lines 4-5 has been amended as follows:

FIGURE 46 presents the light chain variable region sequence of EBV transformant antibody CB2b-G8 (SEQ. ID NO: 17, 18).

The paragraph starting on Page 35, lines 19-20 has been amended as follows:

FIGURE 52 presents the heavy chain variable region sequence of mouse O9 antibody (SEQ. ID NO: 19, 20).

The paragraph starting on Page 35, lines 22-23 has been amended as follows:

FIGURE 53 presents the kappa light chain 1 variable region sequence of mouse O9 variable region sequence of mouse O9 antibody (SEQ. ID NO: 21, 22).

The paragraph starting on Page 35, lines has been amended as follows:

FIGURE 54 presents the kappa light chain 2 variable region sequence of mouse O9 antibody (SEQ. ID NO: 23, 24).

The paragraph starting on Page 35, line 28 has been amended as follows:

FIGURE 55 presents the AKJR4 heavy chain variable region sequence (SEQ. ID NO: 25, 26).

The paragraph starting on Page 35, line 30 has been amended as follows:

(Amended) **FIGURE 56** presents the AKJR4 kappa light chain variable region sequence (SEQ. ID NO: 27, 28).

The paragraph starting on Page 36, line 1 has been amended as follows:

FIGURE 57 presents the CB2iE12 heavy chain variable region sequence (SEQ. ID NO: 29, 30).

The paragraph starting on Page 36, line 3 has been amended as follows:

FIGURE 58 presents the CB2iE12 kappa light chain variable region sequence (SEQ. ID NO: 31, 32).

The paragraph starting on Page 36, line 5 has been amended as follows:

FIGURE 59 presents the CB2iE7 heavy chain variable region sequence (SEQ. ID NO: 33, 34).

The paragraph starting on Page 36, line 7 has been amended as follows:

FIGURE 60 presents the CB2iE7 kappa light chain variable region sequence (SEQ. ID NO: 35, 36).

The paragraph starting on Page 36, line 9 has been amended as follows:

FIGURE 61 presents the MSI 19E5 light chain variable region sequence (SEQ. ID NO: 37, 38).

The paragraph starting on Page 36, line 11 has been amended as follows:

FIGURE 62 presents the kappa light chain 2 of the mouse O4 antibody (SEQ. ID NO: 39, 40).

The paragraph starting on Page 36, line 27 has been amended as follows:

FIGURE 67 depicts the kappa light chain sequence of antibody O4 (SEQ. ID NO: 41, 42).

The paragraph starting on Page 36, line 29 has been amended as follows:

FIGURE 68 depicts the kappa light chain sequence of antibody O1 (SEQ. ID NO: 43, 44).

The paragraph starting on Page 37, line 1 has been amended as follows:

FIGURE 69 depicts the kappa light chain sequence of antibody HNK-1 (SEQ. ID NO: 45, 46).

The paragraph starting on Page 37, line 3 has been amended as follows:

FIGURE 70 depicts the kappa light chain sequence of antibody A2B5 (SEQ. ID NO: 47, 48).

The paragraph starting on Page 37, line 5 has been amended as follows:

FIGURE 71 depicts the Lym 46 heavy chain sequence (SEQ. ID NO: 49, 50).

The paragraph starting on Page 37, line 7 has been amended as follows:

FIGURE 72 depicts the Lym 46 kappa light chain sequence (SEQ. ID NO: 51, 52).

The paragraph starting on Page 40, lines 11-25 has been amended as follows:

Also, the terms "neuromodulatory agent," "autoantibody," "antibody peptide," "peptide," "hapten" and any variants not specifically listed, may be used herein interchangeably, to the extent that they may all refer to and include proteinaceous material including single or multiple proteins, and extends to those proteins having the amino acid sequence data described herein and presented in FIGURES 35-38, 45, 46, 55-61 and 71-72 (SEQ ID NOS:[38, 86,42,87,46,48,50,52,60,62,64,66,68,70,72,96,98] 7, 8, 10, 9, 11, 12, 13, 14, 15, 16, 17, 18, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 49 and 51), and the profile of activities set forth herein and in the Claims. Accordingly, proteins displaying substantially equivalent or altered activity are likewise contemplated. These modifications may be deliberate, for example, such as modifications obtained through site-directed mutagenesis, or may be accidental, such as those obtained through mutations in hosts that are producers of the complex or its named subunits. Also, the terms "neuromodulatory agent," "autoantibody," "antibody peptide," "peptide," "hapten" are intended where appropriate, to include within their scope proteins specifically recited herein as well as all substantially homologous analogs and allelic variations.

The paragraph starting on Page 46, lines 8-16 has been amended as follows:

It should be appreciated that also within the scope of the present invention are DNA sequences encoding an antibody of the invention, or a peptide analog, hapten, or active fragment thereof, which code for a peptide that defines in at least a portion thereof, or has the same amino acid sequence as set forth in FIGURES 35-38, 45, 46, 55-61 and 71-72 (SEQ ID NOS:[38, 86,42,87,46,48,50,52,60,62,64,66,68,70,72,96,98] 7, 8, 10, 9, 11, 12, 13, 14, 15, 16, 17, 18, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 49 and 51), but which are degenerate to the same SEQ ID NOS. By "degenerate to" is meant that a different three-letter codon is used to specify a particular amino acid. It is well known in the art that the following codons can be used interchangeably to code for each specific amino acid:

The paragraph starting on Page 185, lines 18-29 has been amended as follows:

The structures of the IgM heavy and light chains for both the antibodies derived from the EBV-transformants have been determined by analysis of cDNA generated from immunoglobulin mRNA isolated from the cells. The sequences of the heavy and light chain variable regions of MSI 19-D10 and sHIgM22 are provided in **Figures 35-38** (SEQ ID NOS:[46-49] 11, 12, 13, 14 and[38, 40, 41, 42, 44, 45, 86, 87, respectively] 7, 8, 9, and 10). The sequences of the heavy and light chain variable regions of CB2b-G8 are provided in **Figures 45** and **46** (SEQ ID NOS:[50-53] 15, 16, 17, 18). The sequences themselves are not remarkable other than they differ somewhat from known germline immunoglobulin sequences. Thus, they may be the products of somatic diversification during the course of immune responses against unidentified antigens. The value of the sequences is that they provide a blue print for the construction of expression vectors for the production of the immunoglobulin under controlled conditions.

The paragraph starting on Page 185, lines 31-33 and Page 186, lines 1-14 has been amended as follows:

Similarly, the structures of the heavy and light chains from the serum of one of the IgM-producing patients were determined by protein sequence analysis, followed by cloning and

sequence analysis of cDNA from peripheral blood mononuclear cells isolated from the patient. Two closely related heavy and light chains were identified in the patient's serum, designated sHIgM22 (**Figures 35** and **36**) (SEQ ID NOS:[38, 40, 41, 42, 44, 45, 86 and 87] 7, 8, 9, 10). The two heavy and two light chains were both present in the isolated cDNA populations at a ration of 60:40. Both antibodies share a common μ-VDJ rearrangement and λ-VJ rearrangement, indicting that they are derived from a common B cell precursor. They have subsequently diverged, as a result of the accumulation of mutations that have altered the structures of their variable regions. We conclude that both antibodies are expressed in the serum of the patient because peptides from both antibodies were characterized from the protein isolated from the serum. However, the two distinct combinations of variable and light chains were not observed directly, leaving open the possibility that other combinations of the identified heavy and light chains may actually be present. Based on the positions of the observed amino acid substitutions, we suspect that the antibodies have very similar reactivity patterns.

The paragraph starting on Page 188, lines 14-21 has been amended as follows:

The heavy chain variable region of the mouse IgM monoclonal antibody 94.03 was isolated from cDNA by PCR using the RsrII primer ACTCCCAAGTCGGCTCGCTTTCTCTTCAGTGACAAACACAGACATAGAACATTCACC ATGGGATGGAGCTGTATCACT (SEQ ID NO:[76] 53) to introduce the RsrII site upstream of the leader sequence and the PacI primer ACTGACTCTCTTAATTAAGACTCACCTGAGGAGACTGTGAGAGTGGT (SEQ ID NO:[77] 54) to introduce the PacI site while maintaining the correct splice junction at the 3' end of the variable region coding block.

The paragraph starting on Page 189, lines 7-16 has been amended as follows:

The chimeric light chain gene was assembled from two cDNA sequences using the PCR splicing by overlap extension technique (Horton et al. Gene 77:61:1989). The primers flanking the fused regions of the chimeric cDNA (contained the enzyme recognition sequences for the endonuclease Xho I and Nhe I. The 5' primer used to amplify the fused gene product was

TTGGCGCGCCAAAGACTCAGCCTGGACATGATGTCCTCTGCTCAGTTC (SEQ ID NO:[78] 55) ; the 3' primer was ATAGTTTAGCGGCCGCATTCTTATCTAACACTCTCCCCTGTTG (SEQ ID NO:[79] 56). The cDNA coding block was inserted into the light chain cassette vector using these sites.

The paragraph starting on Page 190, lines 1-15 has been amended as follows:

Insertion of sHIgM22 sequences into the expression vector system

The cDNA of mRNA encoding the heavy and light chains of sHIgM22 were prepared by PCR amplification of peripheral blood RNA using 5' primers deduced from amino acid sequence information and sequences in the constant regions of the heavy and light chain respectively. The heavy chain variable region coding block, leader sequence and donor splice junction along with the flanking RsrII and Pac I sites were assembled by using PCR to add the 5' region GACTCGGTCCGCCCAGCCACTGGAAGTCGCCGGTGTTTCCATTCGGTGATCATCACT GAACACAGAGGACTCACCATGGAGTTTGGGCTGAGCTGGGTTTTCCTCGTTGCTCTT TTAAGAGGTGTCCAGTGTCAGGTGCAGCTGGTGGAGTCTGG (SEQ ID NO:[80] 57) and the 3' sequences CCTTAATTAAGACCTGGAGAGGCCATTCTTACCTGAGGAGACGGTGACCAGGGTTC (SEQ ID NO:[81] 58). The resulting DNA molecule was digested with Rsr II and Pac I and subsequently cloned into the expression vector, substituting the desired variable region sequence for the irrelevant sequence in the vector.

The paragraph starting on Page 190, lines 17-22 has been amended as follows:

The light chain sequence was assembled in two steps. The lambda constant region was isolated from mRNA by RT-PCR using the 5' primer CTAGCTAGCGTCCTAGGTCAGCCCAAGGCTGCCCCC (SEQ ID NO:[82] 59) and 3' primer ATAGTTTAGCGGCCGCACCTATGAACATTCTGTAGG (SEQ ID NO:[83] 60). This fragment was cloned using a unique AvrII site and a 3' Not I site into the pCIneo vector.

The paragraph starting on Page 190, lines 24-30 and Page 191, lines 1-5 has been amended as follows:

The variable region of sHIgM22 was generated by RT-PCR using the 5' primer CTAGCTAGCCCGAATTTCGGGACAATCTTCATCATGACCTGCTCCCCTCTCCTCCTCA CCCTTCTCATTCACTGCACAGGGTCCTGGGCCCAGTCTGTGTTGACGCAGCCG (SEQ ID NO:[84] 61) in order to introduce the needed Nhe I site and leader sequence onto the cDNA. The 3' primer, GGGCAGCCTTGGGCTGAGCTAGGACGGTCAGC (SEQ ID NO:[85] 62), was used to introduce an AvrII site so that this fragment could be joined with the constant region piece. The resulting coding block containing a functional leader signal was flanked by the necessary NheI and Xho I sites for cloning into the dHFR/light chain cassette, which was subsequently assembled with the heavy chain plasmid to generate the final product containing both the heavy and light chain coding sequences and promoters needed for expression in mammalian cells.

The paragraph starting on Page 191, lines 25-30 and Page 192, lines 1-6 has been amended as follows:

EXAMPLE 11

IgG_3 ISOTYPE ANTI-OLIGODENDROCYTE MOUSE ANTIBODY O9

The mouse O9 antibody was isolated as an anti-oligodendrocyte antibody and is of the IgG_3 subtype (Kuhlmann-Krieg, S., Sammer, I. and Shachner M. (1988) *Devel Brain Res* **39**:269-280). The O9 antibody binds strongly and specifically to white matter in the CNS. We examined and demonstrated the ability of the O9 antibody to stimulate remyelination in the TMEV model. The O9 antibody heavy chain variable region sequence is provided in **Figure 52** (SEQ ID NOS:[54] 19 and [55] 20). The sequence of the kappa light chain 1 variable region of O9 is provided in **Figure 53** (SEQ ID NOS:[56] 21 and [57] 22). The sequence of the kappa light chain 2 variable region of O9 is provided in **Figure 54** (SEQ ID NOS:[58] 23 and [59] 24).

The paragraph starting on Page 196, lines 24-33 has been amended as follows:

EXAMPLE 14

The sequences of the heavy and light chain variable regions of human antibodies AKJR4, CB2iE12 and CB2iE7, and the light chain variable region of MSI19E5 were determined. The sequences of the heavy and light chain variable region of AKJR4 are shown in **Figures 55** and **56,** respectively (SEQ ID NOS:[60] 25,[61] 26 and[62] 27,[63] 28). The sequences of the heavy and light chain variable region of CB2iE12 are shown in **Figures 57** and **58**, respectively (SEQ ID NOS:[64] 29,[65] 30 and[66] 31,[67] 32). The sequences of the heavy and light chain variable region of CB2iE7 are shown in **Figures 59** and **60**, respectively (SEQ ID NOS:[68] 33,[69] 34 and[70] 35,[71] 36). The sequence of the light chain variable region of MSI19E5 is shown in **Figure 61**, respectively (SEQ ID NOS:[72] 37 and[73] 38).

The paragraph starting on Page 203, lines 19-26 has been amended as follows:

O9 kappa chain sequence:

O9 hybridoma produces two light chains. One of them (noted above and in **FIGURE 53** (SEQ ID NOS:[56] 21 and[57] 22) as "O9 kappa light chain 1") is ubiquitous for all O-series hybridomas and originates from MOPC21 fusion partner. This light chain does not appear to be important for the antibody activity of interest. The sequence of the O9-characteristic kappa chain (noted as "O9 kappa light chain 2" and provided in **FIGURE 54** (SEQ ID NOS:[58] 23 and [59] 24) remains unchanged and is the correct O9 kappa chain sequence.

The paragraph starting on Page 203, lines 28-30 has been amended as follows:

O4 kappa chain sequence:

The correct and complete O4 kappa chain sequence is shown in **FIGURE 67** (SEQ ID NOS:[88] 41 and[89] 42).

The paragraph starting on Page 204, lines 3-6 has been amended as follows:

O1 kappa chain sequence:

This sequence, provided in **FIGURE 68** (SEQ ID NOS:[90] 43 and[91] 44) is completely new. The previously reported O1 kappa chain was the shared MOPC21 kappa chain which is also produced by the O1 hybridoma.

The paragraph starting on Page 204, lines 8-12 has been amended as follows:

HNK-1 kappa chain sequence:

The published HNK-1 sequence and the newly obtained sequence differ in two nucleotides: 174 (G-C) and 281 (C-T, this changes the amino acid from S to F). The changes are highlighted on the sequence provided in **FIGURE 69** (SEQ ID NOS:[92] 45 and[93] 46).

The paragraph starting on Page 204, lines 14-17 has been amended as follows:

A2B5 kappa chain sequence:

This sequence of A2B5 kappa chain shown in **FIGURE 70** (SEQ ID NOS:[94] 47 and [95] 48) is completely new. The previously reported A2B5 kappa chain sequence is in fact the O4 kappa chain sequence.

The paragraph starting on Page 204, lines 23-26 has been amended as follows:

The sequence of LYM46 was determined. The amino acid sequence (SEQ ID NO:[96] 49) and nucleic acid sequence (SEQ ID NO:[97] 50) of the LYM46 heavy chain are depicted in FIGURE 71. The amino acid sequence (SEQ ID NO:[98] 51) and nucleic acid sequence (SEQ ID NO:[99] 52) of the LYM46 heavy chain are depicted in FIGURE 72.

The paragraph starting on Page 205, lines 21-23 has been amended as follows:

The Lym 46 heavy chain variable region sequence was synthesized using overlapping oligonucleotides and cloned into pUDM. The oligonucleotides used were:

5' act ccc aag tcg gtc cgc ttt (SEQ. ID NO: 73)

The paragraph starting on Page 205, lines 25-30 and Page 206, line 1 has been amended as follows:

Template A-- act ccc aag tcg gtc cgc ttt ctc ttc agt gac aaa cac aga cat aga aca ttc acc ATG GAG TTT GGG CTG ACC TGG CTT TCT CTT GTT GCT ATT TTA GAA GGT GTC CAG TGT GAG GTG CAG CTG GTG GAG TCT GGG GGA GGC TTG GTC CAG CCT GGG GGG TCC CTG AGA CTC TCC TGT GCA GCC TCT GGA TTC ACC TTT AGT AGC TAT TGG ATG ACC TGG GTC CGC CAG GCT CCA GGG (SEQ. ID NO: 74)

The paragraph starting on Page 206, lines 3-8 has been amended as follows:

Template B -- CTG GAG TGG GTG GCC AAC ATA AAG AAA GAT GGA AGT GAG AAA TCC TAT GTG GAC TCT GTG AAG GGC CGA TTC ACC ACC TCC AGA GAC AAC GCC AAG AAC TCA CTG TAT CTG CAA ATG AAC AGC CTG AGA GCC GAG GAC ACG GCT GTG TAT TAC TGT GCG AGA CCC AAT TGT GGT GGT GAC TGC TAT TTA CCA TGG TAC TTC GAT CTC TGG GGC CGT GGC ACC CTG GTC ACT GTC TCC TCA ggt gag tct taa tta aga gag tca gt (SEQ. ID NO: 75)

The paragraph starting on Page 206, line 10 has been amended as follows:

3' primer -- act gac tct ctt aat tag (SEQ. ID NO: 76)

The paragraph starting on Page 206, lines 19-21 has been amended as follows:

5' primer containing the leader sequence CTA GCT AGC TCA AGA CTC AGC CTG GAC ATG GTG TTG CAG ACC CAG GTC TTC ATT TCT CTG TTG CTC TGG ATC TCT GGT GCC TAC GGG GAC ATC GTG ATG ACC CAG (SEQ. ID NO: 77)

The paragraph starting on Page 206, line 23 has been amended as follows:

3' primer GAA CGC CTG AGG AGT ATT AT (SEQ. ID NO: 78)

The paragraph starting on Page 207, lines 12-13 has been amended as follows:

5 ' Primer for all human IgG subclasses with Bam HI site:

CTG ATG CTA CGA TGG ATC C GC CTC CAC CAA GGG CCC ATC (SEQ. ID NO: 79)

The paragraph starting on Page 207, lines 15-16 has been amended as follows:

3' Primer for gamma 1, and 2 with Sal 1 site:

GCA TGA GTC TGA CAG CTG TTT ACC CGG AGA CAG GGA GAG GCT (SEQ. ID NO: 80)

IN THE CLAIMS:

The claims have been amended as follows:

6. (Amended) The method of Claim 5 wherein the light chain of said SHIgM22 (LYM22) comprises the amino acid sequence selected from SEQ ID NOS:[42] 10 and[87] 9.

7. (Amended) The method of Claim 5 wherein the heavy chain of said SHIgM22 (LYM22) comprises the amino acid sequence selected from SEQ ID NOS:[38] 8 and[86] 7.

9. (Amended) The method of Claim 8 wherein the light chain of said sHIgM46 (LYM46) comprises the amino acid sequence selected from SEQ ID NO:[98] 51.

10. (Amended) The method of Claim 8 wherein the heavy chain of said sHIgM46(LYM46) comprises the amino acid sequence selected from SEQ ID NO:[96] 49.

40. (Amended) A method according to any of Claims 5, 8, 15, 16, 23, 24, 32, 33, 38 or 39 wherein said monoclonal antibody has an amino acid sequence which corresponds at least in part to an amino acid sequence selected from the group consisting of FIGURE 35 (SEQ ID NO:[38] 8,[86] 7), FIGURE 36 (SEQ ID NO:[42] 10,[87] 9), FIGURE 71 (SEQ ID NO:[96] 49), FIGURE 72 (SEQ ID NO:[98] 51) and active fragments thereof.

45. (Amended) A DNA sequence or degenerate variant thereof, which encodes an antibody, a peptide analog thereof, a hapten corresponding thereto, or an active fragment thereof, selected from the group consisting of:

(A) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 35 (SEQ ID NO:[38] 8,[86] 7);

(B) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 36 (SEQ ID NO:[42] 10, [87] 9);

(C) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 71 (SEQ ID NO:[96] 49);

(D) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 72 (SEQ ID NO:[98] 51);

(E) DNA sequences that hybridize to any of the foregoing DNA sequences under standard hybridization conditions; and

(F) DNA sequences that code on expression for an amino acid sequence encoded by any of the foregoing DNA sequences.

46. (Amended) A recombinant DNA molecule comprising a DNA sequence or degenerate variant thereof, which encodes an antibody, a peptide analog thereof, a hapten corresponding thereto, or an active fragment thereof, selected from the group consisting of:

(A) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 35 (SEQ ID NO:[38] 8,[86] 7);

(B) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 36 (SEQ ID NO:[42] 10,[87] 9);

(C) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 71 (SEQ ID NO:[96] 49);

(D) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 72 (SEQ ID NO:[98] 51);

(E) DNA sequences that hybridize to any of the foregoing DNA sequences under standard hybridization conditions; and

(F) DNA sequences that code on expression for an amino acid sequence encoded by any of the foregoing DNA sequences.

50. (Amended) A unicellular host transformed with a recombinant DNA molecule comprising a DNA sequence or degenerate variant thereof, which encodes an antibody, a peptide analog thereof, a hapten corresponding thereto, or an active fragment thereof, said DNA sequence selected from the group consisting of:

(A) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 35 (SEQ ID NO:[38] 8,[86] 7);

(B) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 36 (SEQ ID NO:[42] 10,[87] 9);

(C) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 71 (SEQ ID NO:[96] 49);

(D) the DNA sequence encoding a protein having a sequence corresponding to at least a portion of FIGURE 72 (SEQ ID NO:[98] 51);

(E) DNA sequences that hybridize to any of the foregoing DNA sequences under standard hybridization conditions; and

(F) DNA sequences that code on expression for an amino acid sequence encoded by any of the foregoing DNA sequences;

wherein said DNA sequence is operatively linked to an expression control sequence.

58. (Amended) The method of Claim 57 wherein said autoantibody has an amino acid sequence which corresponds at least in part to an amino acid sequence selected from the group consisting of FIGURE 35 (SEQ ID NO:[38] 8,[86] 7), FIGURE 36 (SEQ ID NO:[42] 10,[87] 9), FIGURE 71 (SEQ ID NO:[96] 49), FIGURE 72 (SEQ ID NO:[98] 51) and active fragments thereof.

62. (Amended) An antibody produced by injecting a substantially immunocompetent host with an antibody-producing effective amount of an antibody peptide, and harvesting said antibody, said antibody peptide comprising an amino acid sequence selected from the group consisting of FIGURE 35 (SEQ ID NO:[38] 8,[86] 7), FIGURE 36 (SEQ ID NO:[42] 10,[87] 9), FIGURE 71 (SEQ ID NO:[96] 49), FIGURE 72 (SEQ ID NO:[98] 51) and active fragments thereof.